

## **REMARKS**

Claims 1-32 and 39-43 are pending in the application. Applicants appreciate the Examiner's indication that claims 17 and 23-29 would be allowable if rewritten into independent form. Applicants maintain that the remainder of claims are similarly allowable for the reasons discussed below.

Claims 33-38 have been withdrawn and claims 1, 18, 21, and 22 have been amended to address typographical errors and the Examiner's rejections under 35 U.S.C. § 112. Support for the claim amendments may be found throughout the specification, including the claims as originally filed. In particular, support for the amendments to claims 21 and 22 can be found on page 7, lines 13-29. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. Applicants reserve the right to prosecute claims drawn to the originally disclosed or cancelled subject matter in the instant or related patent applications.

### **Rejection of claims under 35 U.S.C. 112, 2<sup>nd</sup> paragraph**

Claims 18-22 have been rejected under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph, as being indefinite. Applicants respectfully traverse the rejection.

Claims 21 and 22 have been amended to more clearly define the phrases "a largest bin" and "a second largest bin." These amendments are believed to obviate the rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 18 has been amended to recite proper antecedent basis. This amendment is believed to obviate the rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

### **Rejection of claims 1-8 and 30-32 under 35 U.S.C. §102(e) as being anticipated by Harari et al. (U.S. Publication No. 2002/0067409)**

Claims 1-8 and 30-32 have been rejected under 35 U.S.C. § 102(e) as being

anticipated by Harari et al., which the Examiner states “discloses a data acquisition and display system applicable to all types of image gathering techniques and that such high precision devices utilize CCD technology”. The Examiner further states that “[t]he images acquired from the first and second image are superimposed one on another for simultaneous visualization” and that Harari et al. indicates that their invention may be used for the analysis of biological samples (i.e., cells and tissue) to visualize transmittance (i.e., intensity) of stains and markers within a cell. Based on these teachings, the Examiner asserts that Harari et al. anticipates the instantly claimed invention. Applicants respectfully traverse the rejection.

For a claim to be anticipated, the prior art reference must teach each and every element set forth in the claim. See MPEP § 2131. Although Harari et al., may disclose superimposing images, it does not, however, teach methods which involve identifying portions of a first image of a cell that corresponds to a defined area; identifying portions of a second image of the cell that corresponds to at least one biomarker and superimposing portions of the second image against portions of the first image to identify whether the biomarker is localized within the defined area as required by independent claim 1.

In addition, Harari et al., does not teach a method of localizing a biomarker by:

accessing a value for each of a plurality of pixel locations of a stained sub-cellular compartment obtained in a first image of a cell;

accessing a value for each of the plurality of pixel locations of a stained biomarker obtained in a second image of a cell; and

subtracting a percentage of the intensity value for each pixel location in the second image from intensity value of the same pixel location in the first image to obtain an adjust intensity value, indicative of the biomarker with the sub-cellular compartment as required by independent claim 30. In fact, the Examiner has acknowledged that Harari et al. does not teach various stains for labeling subcellular compartments as required by independent claim 30.

In contrast, Harari et al. teaches that images may be obtained and subsequently displayed from different scans based on location data in a field of interest such as a microscope slide, stellar images obtained by a telescope, or medical images from CT, NMR or PET scanner. In particular, Harari et al. teaches that it is common to photograph the same region of the sky at different times and to superimpose these images upon one another, where the stellar objects remain fixed and the solar system objects appear and disappear from the stellar background.

In addition to not teaching what is described in independent claims 1 and 30, Harari et al. also does not teach a method for measuring signal intensity on a pixel-by-pixel basis as set forth in claims 2-6 and 30-32, which have further been rejected. In fact, Harari et al. never refers to measuring pixels or pixel intensities nor does it teach or suggest manipulating intensity data.

Further, Harari et al. does not teach methods for reducing out-of-focus elements based on pixel intensities as set forth in claims 7-8. Rather, Harari et al. only teaches that a background color may be deleted (i.e., made transparent) such that two images may be simply placed upon one another so that areas that are stained in both images appear as a mix of the two colors and not the background. This process as taught by Harari et al. is to aid in the process of superimposition for generally comparing two fields as described above and does not teach or suggest how to quantitate pixel intensities of a biomarker with a defined compartment of a cell to determine localization of a biomarker in a cell.

Since Harari et al. does not teach each and every element of the instant claims, Harari et al. does not anticipate the claims and the rejection of claims under 35 U.S.C. § 102(e) should be withdrawn.

**Rejection of claims 1-16, 30-32 and 39-43 under 35 U.S.C. §103(a) as being unpatentable over Harari et al. (U.S. Publication No. 2002/0067409) in view of Dunlay et al. (U.S. Patent No. 6,727,071)**

Claims 1-16, 30-32, and 39-43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Harari et al. in view of Dunlay et al.

The Examiner contends that while Harari et al. indicates that biological samples are typically stained prior to analysis, “Harari et al. fails to provide for various stains for labeling sub-cellular compartments,” while Dunlay et al. “discloses various methodologies for labeling cellular compartments.” Based on the combined teachings of Harari et al. and Dunlay et al., the Examiner asserts that “it would have been obvious to one of skill in the art at the time of the invention to combine the data acquisition and display system of Harari et al. with various sub-cellular compartment stains of Dunlay, thereby performing multiple staining, multiple image acquisition, and multiple image analysis.” Applicants respectfully traverse the rejection.

For a combination of references to render a claim obvious, the combination must teach or suggest each and every element of the claim at issue. Further there must be some suggestion or motivation in the references themselves or in the general knowledge of the skilled person to modify or combine the reference teaching so as to produce the claimed invention, and there must be a reasonable expectation of success. See MPEP § 2143.

For there to be a motivation to combine the references, there must be a suggestion in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine the two references. As described above, Harari et al., does not teach or suggest, either explicitly or implicitly, imaging subcellular structures of cells and imagining biomarkers in cells and superimposing the images to determine if the biomarker is localized within the cell as described in the present claims. Although Dunlay et al. provides an independent method for analyzing biomarkers in cells (described further below), there is no suggestion in either the Harari et al. or Dunlay et al., references for the teachings of the two to be combined. In fact, since Dunlay et al., teaches an independent method, one would not need to attempt to combine its teachings with Harari to result in a method for localizing a biomarker within a cell.

Notwithstanding the lack of motivation to combine, the combined teachings of Harari et al. and Dunlay et al. do not teach what is defined by the present claims. Although Harari et al. may teach a data acquisition and display system, as discussed above, Harari et al. does not teach a method of localizing a biomarker to a subcellular

compartment in a cell by superimposing an image of the biomarker with an image of a subcellular component. While Dunlay et al. teaches a variety of subcellular markers, it also does not teach or suggest a method of identifying the intensity of particular markers to identify subcellular compartments, such as the cell nucleus or cytoplasm. Rather, Dunlay et al. teaches a method that relies on obtaining average measurements of a labeled biomarker in two different subcellular compartments and determining the differential intensities of the labeled biomarker in the two locations (e.g., the NucCyt difference). Thus, one of skill of the art would not arrive at the instant claimed methods based on the teachings of Harari et al. and Dunlay et al.

Prima facie obviousness cannot be established in the absence of some motivation or suggestion in the prior art to modify or combine the cited prior art teachings so as to arrive at the claimed invention and it cannot be established where the proposed combination fails to disclose or suggest all limitations of the claimed subject matter. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

### CONCLUSION

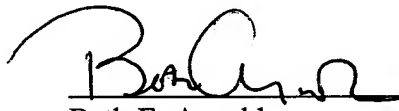
For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and notification of such is respectfully requested.

Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this application be charged to Deposit Account Number **06-1448, Reference YUA-001.01**.

If, for any reason, a telephonic conference with the Applicants would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Agent at the telephone number provided below.

Respectfully submitted,  
FOLEY HOAG LLP

Dated: June 30, 2005

  
Beth E. Arnold  
Reg. No. 35,430  
Attorney for Applicants

**Customer No.: 25181**  
Patent Group  
Foley Hoag LLP  
World Trade Center West  
155 Seaport Boulevard  
Boston, MA 02210

Telephone: (617) 832-1294  
Facsimile: (617) 832-7000